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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/076,288	02/19/2002	Shiao-Wen Tsai	BHT-3111-234	1092
7590 07/02/2004 DOUGHERTY & TROXELL SUITE 1404 5205 LEESBURG PIKE FALLS CHURCH, VA 22041			EXAMINER MOHAMED, ABDEL A	
			ART UNIT 1653	PAPER NUMBER

DATE MAILED: 07/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/076,288	TSAI ET AL.	
	Examiner	Art Unit	
	Abdel A. Mohamed	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 March 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-24 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-24 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

ACKNOWLEDGMNT FOR PRIORITY, STATUS OF THE APPLICATION AND CLAIMS

1. Acknowledgment is made of Applicant's claim priority based on Chinese Application No. 090119567 having a filing date of 8/10/01. Receipt is acknowledged of papers submitted under 35 U.S.C. § 119, which papers have been placed of record in the file. Claims 1-24 are present for examination.

THE SPECIFICATION, CLAIMS AND ABSTRACT ARE A LITERAL TRANSLATION

2. A substitute specification including claims and abstract in proper idiomatic English and in compliance with 37 CFR 1.52(a) and (b) is required. The claims are generally narrative and indefinite and fail to conform to current U.S. practice. They appear to be a literal translation into English from a foreign document and are replete with grammatical and idiomatic errors.

NUMEROUS ERRORS IN THE SPECIFICATION

3. 35 U.S.C. 112, first paragraph, requires the specification to be written in "full, clear, concise, and exact terms." The specification is replete with terms, which are not clear, concise and exact. The specification should be revised carefully in order to comply with 35 U.S.C. 112, first paragraph. Examples of some unclear, inexact or verbose terms used in the specification are: pages 1, 2 and 9 are fragmented sentences in general; page 1, line 3, "...that formed by various rates...."; page 2, lines 7 and 8

".....nationally occurring in body"; page 2, lines 34 and 35, "...gelatin is also with good bio-compatibility and biodegradation in the body"; page 9, line 7, "and then can be process to different types...."; page 9, lines 10 and 11, "and fine physics of impalpable bio-composite is formed"; page 9, lines 23 and 24, "...with carbodiimide in the little acid of organic solution"; and page 9, line 30, ".....this invention are also never have described in previous study" .

CLAIMS REJECTION-35 U.S.C. § 112^{2nd} PARAGRAPH

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Independent claim 1 is indefinite and confusing because the preamble of the claim is not commensurate with the body of the claim. That is, the preamble recites a method for producing cross-linked polysaccharide-protein bio-composites while the body of the claim is devoid of any positive methods except for disclosing the weight ratio of polysaccharide and protein solution, the pH range and reciting that the cross-linking reaction is processed in the water/organic solution that contains the cross-linked reagent. Further, it is not understood how the cross-linking reaction is processed? Is it in water solution or organic solution or both. Appropriate clarification is required.

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Claim 1, line 2 is grammatically indefinite in the recitation "comprising the type of:". It is believed to be typographical error. Amendment of the claim to recite "comprising the steps of" is suggested.

Claim 1 recites the limitations "the polysaccharide solution", "the weight ratio", "the cross-linking reaction" and "the water/organic solution" in lines 3, 4 and 7, respectively. There are insufficient antecedent basis for these limitations in the claim.

Claim 1 is indefinite in the recitation "and hydroxyl compound". What does this mean? Should the "and" be "with". Appropriate clarification is required.

Claim 1 and 19-23 are indefinite in the recitation "water/organic solution" because the claims contain the use of an alternative expression wherein the limitation covers two different elements, i.e., "water" is not the same as "organic" and vice versa. Amendment of the claims to recite "water or organic" or "water and organic" is suggested.

Claims 2-5, 10, 17, 19 and 21 are indefinite in the recitation "wherein said step (a)" claims 2 and 3; "wherein said step (b)" claims 4, 5 and 10; and "wherein said step (c)" claims 17, 19 and 21, respectively because claims 2-5, 10, 17, 19 and 21 depend on claim 1 and there are no steps (a), (b) and (c) recited in claim 1. Appropriate correction is required.

Claims 3, 5 and 24 are indefinite in the recitation "the mixture of both" because it is unclear as to the amounts of the components in the mixtures. Appropriate clarification is required. Also, there is no antecedent basis for "the mixture". Amendment of the claims to recite "a mixture" is suggested.

Claims 3-24 are indefinite in the recitation "The method claim....". Amendment of the claims to recite "The method of claim...." would obviate this rejection.

Claim 4 is indefinite in the recitation "hydrogen chloride". Amendment of the claim to recite "hydrochloric acid" is suggested.

Claim 5 is indefinite and confusing in the recitation "hydroxyl group donor of alkalinity" because it is not clear how is alkalinity donated"? Appropriate clarification is required.

Claim 6 is indefinite in the recitation "wherein said the solution is that collagen is dissolved at pH3 solution...". Amendment of the claim to recite "wherein protein solution is collagen dissolved at pH 3..." is suggested. Also, it is not understood what is meant by "while the solution is made of polysaccharide solution" because it is not clear how a collagen dissolves while the solution is made of polysaccharide solution? Appropriate clarification is required.

Claims 6-9 are indefinite in the recitation "wherein said the protein solution". Amendment of the claims to recite "wherein said protein solution" is suggested.

There are no active method step(s) recited in claims 6-14 and 16. Although, the claims state "dissolved" (claims 6-9), "adjusted" (claims 9 and 10), "formed, degassed or cast" (claims 11-14) and "mixed" (claim 16), respectively but, the claims do not use active method steps (i.e., dissolving, adjusting, forming, degassing, casting and mixing). Thus, there is inconsistency with independent claim 1, which uses active method steps (i.e., preparing, adjusting and processing) as such, dependent claims 6-14, and 16 are indefinite. Appropriate correction is required.

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Claims 7 and 8 are indefinite in the recitation "after mixing the both solutions".

Amendment of the claims to recite "after mixing both solutions" would obviate this rejection.

Claims 7 and 8 are indefinite in the recitation "wherein said the protein solution is that collagen is dissolved....". Amendment of the claim to recite "wherein said protein solution is collagen dissolved in....." is suggested. There is inconsistency between claim 7 and 8 because claim 7 recites the protein solution is collagen dissolved in alkaline while claim 8 recites the protein solution is collagen dissolved in acid. Appropriate correction is required.

Claim 9 is indefinite in the recitation "wherein said the protein solution is that gelatin is dissolved in de-ionized water, and ion strength...". Amendment of the claim to recite "wherein said protein solution is gelatin dissolved in de-ionized water, and the ionic strength..." is suggested. It is not clear to what value the ionic strength is adjusted by sodium chloride? Appropriate clarification is required.

Claim 10 is indefinite and vague in the recitation "the mixture solution is adjusted by acid and hydroxyl compound". It is not clear how the solution is adjusted because one is acid and the other is base. Appropriate clarification is required.

In claim 10, the word "proposity" is misspelled? Amendment of the claim to recite "porosity" is suggested.

Claims 10 and 14 are indefinite in the recitation "using the squeezer equipment" and "the squeezer apparatus", respectively because it is not clear what is the squeezer

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equipment or apparatus? since it is not defined in the specification or in the claim.

Appropriate clarification is required.

Claim 10 recites the limitation "the squeezer equipment" in line 5. There is insufficient antecedent basis for this limitation in claim 10 or claim 1.

Claim 11 recites the limitation "the film matrix" in line 1. There is insufficient antecedent basis for this limitation in claim 11 or claim 10 or claim 1.

Claims 12 and 13 recite "and allows to vacuum dry under freeze-dry drying...". It is redundant. Amendment of the claims to recite "and freeze-drying...." is suggested.

Claim 12 is indefinite and confusing in the recitation the phrase "the porosity of matrix is in the form of a pore morphology with the interconnectivity structure". It is not clear what the phrase means? Appropriate clarification is required.

Claim 14 recites the limitations " the coagulant of organic solvent" and "the squeezer apparatus" in lines 2 and 3, respectively. There are insufficient antecedent basis for these limitations in claim 14 or claim 10 or claim 1.

Claim 14 is indefinite in the recitation the acronym "HA". Use of the full terminology at least in the first occurrence would obviate this rejection.

Claim 15 recites the limitations " said coagulant", "organic solvent", "the mixture" and "the weight fraction" in lines 1, 2 and 6, respectively. There are insufficient antecedent basis for these limitations in claim 15 or claim 14 or claim 10 or claim 1.

Claims 15 and 16 are indefinite in the recitation "60% and 100%" and "75% and 100%", respectively because it is not clear as to what mole %. Is it w/v or w/w or v/v? Appropriate clarification is required.

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Claim 16 is indefinite and confusing in the recitation "can be mixed with any ratio". Does this include 0%:0%? Appropriate clarification is required.

Claim 16 recites the limitation "the ketones and alcohol" in line 1. There is insufficient antecedent basis for this limitation in claim 16 or claim 15 or claim 14 or claim 10 or claim 1.

Claim 17 recites the limitation "the cross-linking agent" in line 1. There is insufficient antecedent basis for this limitation in claim 17 or claim 1.

Claims 15 and 18 are indefinite in the recitation "the mixture of each organic solvent" (claim 15) and "the mixture of each group" (claim 18) because it is unclear as to what are the mixtures? Amounts of the components in the mixtures? and which components? Further, the use of "each" is not appropriate for a Markush species. Appropriate correction is required.

Claims 19, 20, 22 and 23 are grammatically indefinite in the recitation the phrase "water of ethanol or acetone solution". Appropriate correction is required.

Claim 21 recites the limitation "the salt solution" in line 3. There is insufficient antecedent basis for this limitation in claim 21 or claim 1.

Claim 21 is indefinite and confusing in the recitation "washing with distilled water after immersing in the salt solution" because it is not clear what is immersed? Is it the method or the composition? Appropriate clarification is required.

Claim 24 is indefinite in the recitation "wherein said the salt solution". Amendment of the claims to recite "wherein said salt solution" is suggested provided there is proper antecedent basis in claim 21.

CLAIM REJECTIONS-35 U.S.C. § 102(b)

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) The invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 17 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Feijen (U.S. Patent No. 5,041,292).

The prior art of Feijen et al. discloses a biodegradable hydrogel matrix comprising a protein, a polysaccharide such as chondroitin sulfate and a cross-linking agent, wherein the cross-linking agent is a carbodiimide, preferably a water-soluble carbodiimide N-(3-dimethylaminopropyl)-N-ethylcarboimide (EDC). The cross-linking agent is added to an aqueous solution of the polysaccharide and protein, at an acidic pH. The cross-linking agent providing network linkages there between, wherein the weight ratio of polysaccharide to protein in the matrix is in the range 10:90 to 90:10 which overlaps with the claimed ranges of 20/80 to 80/20 (See e.g., cols. 2-4, Example 1, claims 1, 6 and 12) as directed to claims 1, 2, 17 and 18, and as such the prior art anticipates the claims as drafted.

CLAIMS REJECTION-35 U.S.C. § 103(a)

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Silver et al. (U.S. Patent No. 4,970,298) taken with Feijen (U.S. Patent No. 5,041,292) and Silver et al. (U.S. Patent No. 4,703,108).

The reference of Silver et al. '298 patent discloses a method for the producing cross-linked protein-polysaccharide bio-composite comprising a collagen-based solution or an insoluble collagen dispersed and swollen in suitable liquid media (e.g., dilute hydrochloric acid, dilute acetic acid or the like) at a pH between 3.0 and 5.0 and is subjected to a temperature of between 0⁰ C to -100⁰ C to thereby solidify the collagen-based material. The solidified collagen-based material is subjected to a vacuum of less

than about 50 millitor at a temperature of from about 22⁰ C to -100⁰ C to form a collagen based sponge or the collagen-based dispersion is dried into sheet form at temperatures of from 4⁰ C to 40⁰ C for a period of time of from 2 to 48 hours. The collagen-based sponge or sheet is contacted with cross-linking agent of a carbodiimide which include 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide, wherein the collagen-based sponge or sheet is immersed in a carbodiimide solution at a concentration of from about 0.1 to 10% (W/V) and maintained at a temperature of from about 2⁰ C to 40⁰ C and at a pH of between 2 to 11 for a period of time of from about 2 to 96 hours to form the collagen-based matrix. The carrier compound (intermediate) polysaccharide such as hyaluronic acid are incorporated during the initial processing steps in forming the collagen-based sponge or sheet, or after cross-linking of the intermediate collagen-based matrix or after mixing with collagen during dispersion, prior the cross-linking steps (See e.g., cols.4-6, Examples 4, 8 and 11) as directed to claims 1-4, 6-8, 10-13 and 17-21. On col. 7, lines 1-4, the '298 patent states that a film 0.5 to 1.5 mm in thickness is applied to the matrix layer and is allowed to cure at a room temperature for at least 2 hours using a vacuum of 14 in of Hg, which overlaps with the claimed matrix thickness of 50 μ m-1mm thickness of claim 14. Further, as to the limitation using organic solvents such as ethanol of claims 15, 22 and 23, the '298 patent discloses using organic solvent such as ethanol in the process of producing a collagen-based matrix. Also, on Example 1, the reference discloses the use of acetic acid and NaCl in the process of preparing soluble and insoluble collagens, and as such meet the limitations of claims 4 and 5.

The reference of Silver et al. '298 patent differs from claims 1-24 in not teaching the weight ratio of polysaccharide and protein which is in the range of 20/80 to 80/20 and use of a buffer solution of phosphate and NaCl having a concentration of 0.15-4M.

However, the secondary reference of Feijen et al. as discussed above under the rejection of 102(b) discloses a biodegradable hydrogel matrix comprising a protein, a polysaccharide such as chondroitin sulfate and a cross-linking agent, wherein the cross-linking agent is a carbodiimide, preferably a water-soluble carbodiimide N-(3-dimethylaminopropyl)-N-ethylcarboimide (EDC). The cross-linking agent is added to an aqueous solution of the polysaccharide and protein, at an acidic pH. The cross-linking agent providing network linkages there between, wherein the weight ratio of polysaccharide to protein in the matrix is in the range 10:90 to 90:10 which overlaps with the claimed ranges of 20/80 to 80/20 (See e.g., cols. 2-4, Example 1, claims 1, 6 and 12) as directed to claims 1, 2, 17 and 18. Further, the secondary reference of Silver et al. '108 patent discloses the formation of a sponge or a sheet of collagen-based matrix incorporating polysaccharide such as hyaluronate, wherein the soluble collagen is dissolved in a suitable solvent, such as dilute HCL acid, dilute acetic acid or the like (See e.g., cols. 3-4) as directed to claim 4. On Example 19, the reference teaches the use of buffer solution having a concentration of 0.182M phosphate and 0.154M NaCl, which overlaps with the buffer salt concentration of 0.154M of claim 24.

Thus, the combined teachings of the prior art clearly teaches a method for producing biodegradable collagen-based matrix in sponge or sheet form, wherein polysaccharide such as hyaluronic acid and collagen are added to a dilute HCl solution of pH 3. The solution is poured into a vacuum flask and de-aerated (degassed) at a vacuum, and then cross-linked with carbodiimide and allowed to air dry or freeze dry for a period of time under suitable conditions to form the collagen-based matrix. Therefore, in view of the above, the combined teachings of the prior art makes *prima facie* obvious the claimed invention's method for the producing cross-linked polysaccharide-protein bio-composites such as cross-linked hyaluronic acid-collagen biocomposites,

particularly, to homogenous solution that is formed by various concentrations of hyaluronic acid-protein, and can be processed to different types of the bio-composites as claimed in claims 1-24, absent of sufficient objective factual evidence or unexpected results to the contrary.

CONCLUSION AND FUTURE CORRESPONDANCE

7. No claim is allowed.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed whose telephone number is (571) 272-0955. The examiner can normally be reached on Monday through Friday from 7:30 a.m. to 5:00 p.m. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher S.F. Low can be reached on (571) 272-0951. The appropriate fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306 for regular communications and (703) 305-7401 for After Final communications..

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

 Mohamed/AAM

June 25, 2004


CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600